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A61K 31/47

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(54) **2,2'-Alkylenediindole derivatives, process for their production, medicines containing them and their use as anti-ulcer agents**

2,2'-Alkylenediindolderivate, Verfahren zu ihrer Herstellung, sie enthaltende Arzneimittel und deren Verwendung als Ulcusterapeutikum

Dérivés de 2,2'-alkylenediindole, procédé pour leur production, médicaments les contenant et leur utilisation comme agents à activité anti-ulcéraire

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**EP 0 537 532 B1**

## Description

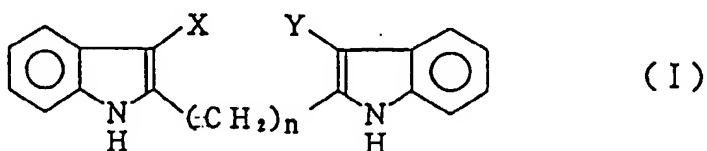
This invention relates to the use of indole derivatives for the preparation of pharmaceutical compositions for the treatment of ulcers. Further, it relates to new indole derivatives and pharmaceutical compositions comprising them.

Known medicaments which have been used as antiulcer agents include  $H_2$ -receptor antagonists representative of which is cimetidine, gastric acid secretion inhibitors such as omeprazole inhibiting proton pump ( $H^+$ ,  $K^+$ -ATPase) and medicaments having gastric mucosa protection activity, which are chosen depending on the symptom of patients. However those medicaments are of such disadvantages as generally weak activity and occurrence of side effects. For instance, cimetidine, representative of  $H_2$ -receptor antagonists have encountered the presence of intractable ulcer. Omeprazole has suffered from the occurrence of carcinoid and the interaction with other drugs including diazepam and phenytoin such as a lowering of hepatic clearance. Thus there is a continuing need for effective antiulcer agents.

JP-A-03 284 622 (published at 16.12.91) describes the synthesis of 3,3'-di(2-(2-pyridyl)ethyl)-2,2'-(1,4-dicyano) tetramethylenediindole and its use as  $H^+$ / $K^+$ -ATPase inhibitor.

The present invention results from efforts to develop new indole derivatives with more improved antiulcer effect.

One object of the invention is the use of a compound of formula (I)



wherein

X and Y each independently represent H or  $-CH_2CH_2R$ ;

R represents pyridyl or substituted amino of  $NR_1R_2$ ;

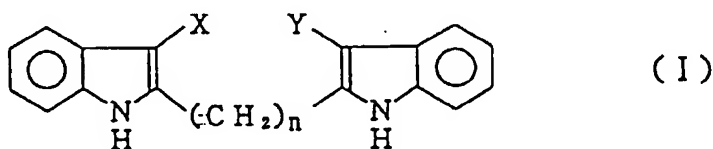
$R_1$  represents H or  $C_1-C_6$  alkyl;

$R_2$  represents 2-(3-indolyl)ethyl, benzyl, phenylethyl, phenylpropyl or phenylbutyl; or

$R_1$  and  $R_2$  together with the nitrogen atom to which they are attached may form an N-containing 5 to 6 membered hetero ring, an N, O-containing hetero ring, which hetero ring may be fused with benzene; n is an integer of 4 to 8;

with the proviso that X and Y both do not represent H or piperidinoethyl when n is 4, or a pharmaceutically acceptable acid addition salt thereof, for the preparation of pharmaceutical compositions for the treatment of ulcers.

According to another aspect, the invention refers to new indole derivatives of formula (I)



wherein

X and Y each independently represent H or  $-CH_2CH_2R$ ;

R represents pyridyl or substituted amino of  $NR_1R_2$ ;

$R_1$  represents H or  $C_1-C_6$  alkyl;

$R_2$  represents 2-(3-indolyl)ethyl, benzyl, phenylethyl, phenylpropyl or phenylbutyl; or

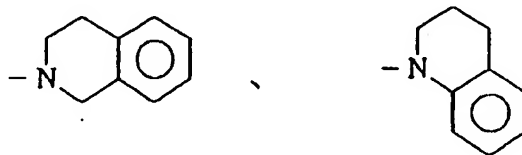
$R_1$  and  $R_2$  together with the nitrogen atom to which they are attached may form an N-containing 5 to 6 membered hetero ring, an N, O-containing hetero ring, which hetero ring may be fused with benzene; n is an integer of 4 to 8;

with the proviso that X and Y both do not represent H or piperidinoethyl when n is 4 and that X and Y both do not represent H when n is 5 or 8, or a pharmaceutically acceptable acid addition salt thereof.

Suitable pharmaceutically acceptable acid addition salts of the compounds of formula (I) include acid addition salts

formed with organic or inorganic acids such as hydrochlorides, hydrobromides, sulfates, phosphates, acetates, succinates, citrates, tartrates, fumarates and maleates.

In the definition of formula (I), C<sub>1</sub>-C<sub>6</sub> alkyl represented by R<sub>1</sub> includes, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl and n-hexyl. When R<sub>1</sub> and R<sub>2</sub> together with the nitrogen atom to which they are attached form an N-containing 5 to 6 membered hetero ring or an N, O-containing hetero ring, the 5 to 6 membered hetero ring includes e.g., pyrrolidine and piperidine and the N, O-containing hetero ring includes e.g., morpholine. When those hetero rings are fused with benzene, the fused ring includes e.g.,

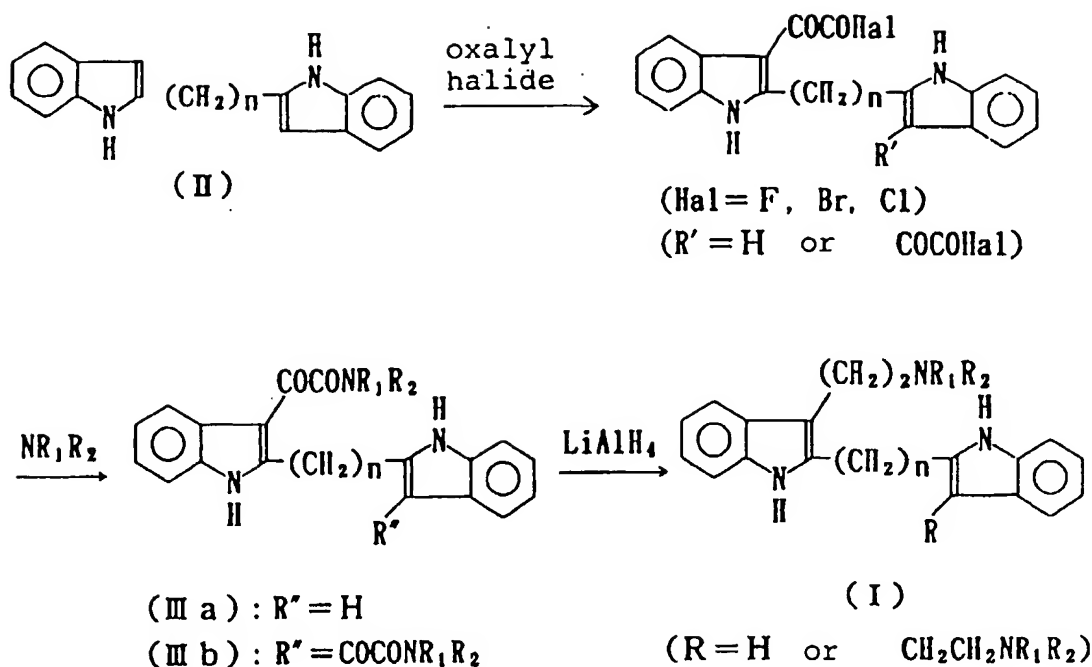


Representative compounds of formula (I) are listed below.

3,3-Di(2-piperidinoethyl)-2,2'-hexamethylenediindole,  
 3-(2-Piperidinoethyl)-2,2'-hexamethylenediindole,  
 3-(2-Phenethylaminoethyl)-2,2'-tetramethylenediindole,  
 3-(2-Piperidinoethyl)-2,2'-octamethylenediindole,  
 3-(2-Morpholinoethyl)-2,2'-tetramethylenediindole,  
 3-(2-Piperidinoethyl)-2,2'-tetramethylenediindole,  
 3,3'-Di(2-benzylaminoethyl)-2,2'-tetramethylenediindole,  
 3-(2-Benzylaminoethyl)-2,2'-tetramethylenediindole,  
 3,3'-Di(2-(1,2,3,4-tetrahydroisoquinolin-2-yl)ethyl)-2,2'-tetramethylenediindole,  
 3-(2-(1,2,3,4-Tetrahydroisoquinolin-2-yl)ethyl)-2,2'-tetramethylenediindole,  
 3,3'-Di(2-pyrrolidinoethyl)-2,2'-tetramethylenediindole,  
 3-(2-Piperidinoethyl)-2,2'-tetramethylenediindole,  
 3,3'-Di(2-phenethylaminoethyl)-2,2'-tetramethylenediindole,  
 3,3'-Di(2-(1,2,3,4-tetrahydroquinolin-1-yl)ethyl)-2,2'-tetramethylenediindole,  
 3-(2-(1,2,3,4-Tetrahydroquinolin-1-yl)ethyl)-2,2'-tetramethylenediindole,  
 3-(2-(2-(3-Indolyl)ethylamino)ethyl)-2,2'-tetramethylenediindole,  
 3,3'-Di(2-(N-methylbenzylamino)ethyl)-2,2'-tetramethylenediindole,  
 3-(2-(N-Methylbenzylamino)ethyl)-2,2'-tetramethylenediindole,  
 3,3'-Di(2-(3-phenylpropylamino)ethyl)-2,2'-tetramethylenediindole,  
 3-(2-(3-Phenylpropylamino)ethyl)-2,2'-tetramethylenediindole,  
 3,3'-Di(2-(4-phenylbutylamino)ethyl)-2,2'-tetramethylenediindole,  
 3-(2-(4-Phenylbutylamino)ethyl)-2,2'-tetramethylenediindole,  
 3,3'-Di(2-(2-pyridyl)ethyl)-2,2'-tetramethylenediindole.

The compounds of formula (I) can be prepared in accordance with known methods as shown in Scheme I, for instance using the methods mentioned in M. Julia et al. Bull. Chim. Soc. France, 1953-1956 (1964) or Sakai et al. Yakugaku Zasshi 95, 1152-1160 (1975).

Scheme I



The starting bisindole compound of formula (II) is reacted with an oxalyl halide, e.g., oxalyl chloride in an inert solvent such as ether or tetrahydrofuran. After isolation or without isolation of the reaction product, it is reacted with an amine to prepare a glyoxylamide of formula (IIIb). The reaction is usually carried out at a temperature in the range of 0°C to room temperature. In that case, the compound of formula (IIIa) wherein only once of the indoles rings is substituted can be produced by controlling the amount of oxalyl halides used. A preferred amount of the halides used is 1 to 2 equivalents. Subsequently, the amide of formula (III) is reduced with lithium aluminium hydride to give the corresponding amine of formula (I).

Alternatively, the compound of formula (I) wherein R is pyridyl can be prepared in accordance with a known method (A.P. Gray et al. JACS 79 (1957) 3554), for instance by reacting the starting bisindole compound with the corresponding vinylpyridine in acetic acid. A preferred reaction temperature is from room temperature to a reflux temperature of the solvent used.

The compounds of formula (I) and their pharmaceutically acceptable salts exert an anti-secretory effect by inhibition of H<sup>+</sup>/K<sup>+</sup> ATPase and are useful as an antiulcer agent.

Thus the invention also provides a pharmaceutical composition which comprises as an active ingredient an effective amount of the novel compounds of formula (I) or pharmaceutically acceptable acid addition salts thereof. Such compositions may be formulated in conventional manner using one or more pharmaceutically acceptable carriers and/or excipients.

The compounds of formula (I) and their pharmaceutically acceptable salts inhibit exogenously and endogenously stimulated gastric acid secretion and are useful as an antiulcer agent in the treatment of gastrointestinal diseases such as gastric and duodenal ulcers, gastritis, reflux esophagitis and Zollinger-Ellison Syndrome.

The indole derivatives can usually be administered orally or parenterally in the form of various pharmaceutical preparations. For oral administration, the pharmaceutical compositions may take the form of solid preparations including tablets such as sugar-coated tablets, capsules such as soft and hard capsules and liquid preparations such as solutions, emulsions or suspensions. For parenteral administration, the compositions may take the form of injections. Such solid preparations can be prepared by conventional means with pharmaceutically acceptable excipients such as binding agents, fillers, lubricants, disintegrants or wetting agents. Such liquid preparations can be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents, emulsifying agents, non-aqueous vehicles and preservatives. The preparations may also contain buffer salts, flavoring, coloring and sweetening agents if desired.

The active ingredient is contained in the formulation in an amount of 0.1-100% by weight, suitably 1-50% by weight in the case of formulations for oral administration and 0.2-20% by weight in the case of formulations for injection based

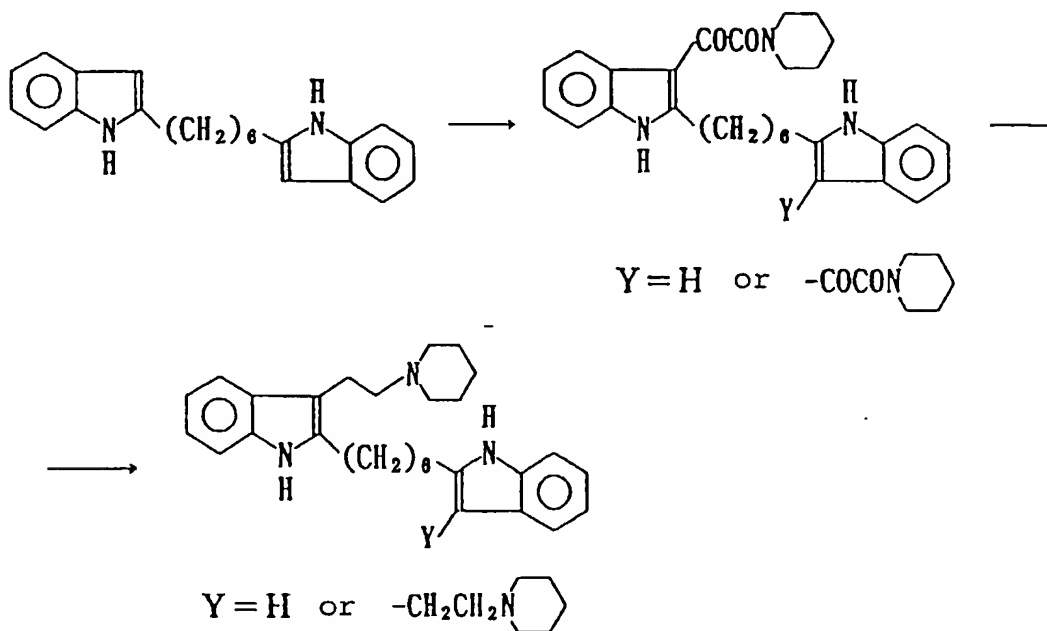
on the weight of the formulation.

Route and dosage of administration for the compounds of the invention are not specifically limited and are appropriately chosen depending upon form of the formulation, age and sex of the patient, severity of the disease and other factors. Daily dosage of the active ingredient is 1 mg to 2000 mg.

The invention is further illustrated by the following examples.

#### Example 1

##### 3,3'-Di(2-piperidinoethyl)-2,2'-hexamethylenediindole



(1) Hexamethylene-2,2'-bisindole (3.21 g) was added to anhydrous ether. Oxalyl chloride (1.8 ml) was added dropwise under ice-cooling and stirring was continued for 2 hrs. Then piperidine (5.0 ml) was added and further stirring was continued for 2 hrs. The reaction solution to which was added water was extracted with chloroform, washed with diluted hydrochloric acid and 10% sodium carbonate solution and dried over sodium sulfate. The crude product was purified by column chromatography on silica gel.

Eluates with 20% ethyl acetate/chloroform afforded 0.88 g of monoglyoxylamide (Y=H) and eluates with 50% ethyl acetate/chloroform afforded 2.25 g of diglyoxylamide



(2) Diglyoxylamide (2.25 g) and lithium aluminum hydride (1.0 g) were added to anhydrous THF and the mixture was heated at reflux for 5 hrs. After ice-cooling, unreacted lithium aluminum hydride was decomposed with 10% aqueous NaOH solution and filtered. Evaporation of the solvent gave 2.0 g of the title compound as a solid, m.p. 79-83°C.

PMR (CDCl<sub>3</sub>,  $\delta$ ) 1.25 -1.95(20H,m), 2.40 -3.00(24H,m), 7.00 -7.17(4H,m), 7.20 -7.32(2H,m), 7.45 -7.56(2H,m), 8.46(2H,brs)

MASS(EI) 538(M<sup>+</sup>), 453, 440, 98(100)

## Example 2

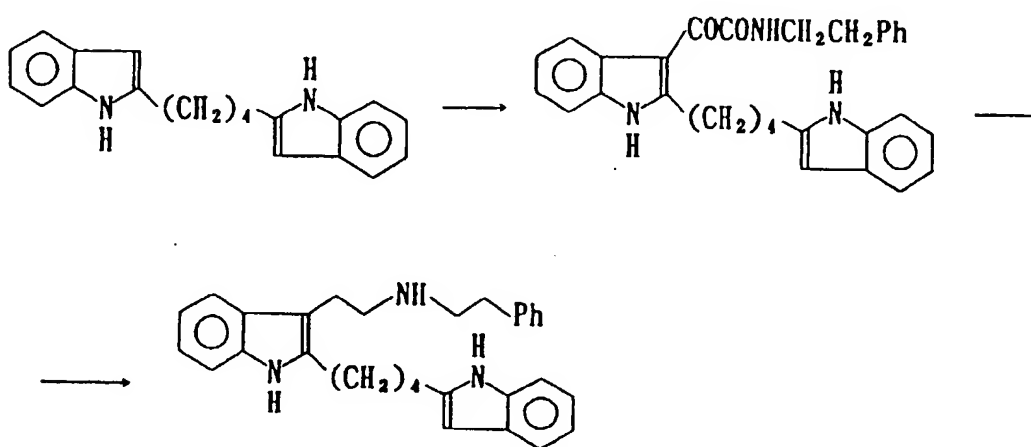
## 3-(2-Piperidinoethyl)-2,2'-hexamethylenediindole

Monoglyoxylamide (0.88 g) obtained in Example 1(1) was reacted in a similar manner to that mentioned in Example 1(2). The crude product was purified by column chromatography on silica gel. Eluates with 10% ethanol/chloroform afforded 0.30 g of the oily monoamine (title compound).

PMR (CDCl<sub>3</sub>, δ) 1.18-1.85(14H,m), 2.40-2.12(10H,m), 2.80-3.02(2H,m), 6.19(1H,s), 6.97-7.25(6H,m), 7.42-7.56(2H,m), 7.85(1H,brs), 8.52(1H,brs)  
 MASS(EI) 427(M<sup>+</sup>), 329, 98(100)

## Example 3

## 3-(2-Phenethylaminoethyl)-2,2'-tetramethylenediindole



Oxalyl chloride (0.65 ml) was added dropwise under ice-cooling to a THF solution of tetramethylene-2,2'-bisindole (2.0 g). 30 minutes later, 2-phenylethylamine (3.36 g) was added and stirring was continued for 1.5 hrs. The reaction solution to which chloroform was added was washed with diluted hydrochloric acid and brine and then dried over sodium sulfate. The crude product was purified by column chromatography on silica gel. Eluates with chloroform/ethyl acetate (2/1) afforded 0.66 g of glyoxylamide.

To a dioxane solution of glyoxylamide (0.66 g) was added under ice-cooling lithium aluminum hydride (0.66 g) and the mixture was heated at reflux for 5 hrs. Under ice-cooling, unreacted lithium aluminum hydride was decomposed with water and 15% aqueous NaOH solution and filtered. The crude product was purified by column chromatography on silica gel. Eluates with chloroform/methanol (5/1) afforded 0.51 g of the oily title compound.




PMR (CDCl<sub>3</sub>, δ) 1.69(5H, brs), 2.6 - 2.8(6H, m), 2.8 - 2.95(6H, m), 6.21(1 H, s), 7.00 - 7.30(11H, m), 7.51(2H, d, J = 7Hz), 7.67(1H, s), 8.23(1H, s)  
 MASS(EI) 435(M<sup>+</sup>), 303, 157, 134, 105(100)






## Examples 4-22

In a similar manner to those mentioned in Examples 1 and 2, the following compounds were prepared from the corresponding amine starting materials.





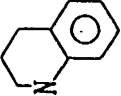
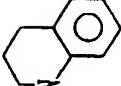
### Example

No.	n	X	Y	Appearance	PMR (CDCl <sub>3</sub> , δ), MASS(EI)
4	8		H	Oily	1.25-1.85(18H, m), 2.50-2.80(10H, m), 2.90-2.98(2H, m), 6.21(1H, s), 7.0-7.15(4H, m), 7.52(2H, d, J=8Hz), 7.76(1H, brs), 8.10(1H, brs) 456(M <sup>+</sup> +1), 358, 98(100)
5	4		H	Oily	1.70(4H, brs), 2.0-2.38(6H, m), 2.60-2.8(4H, m), 2.80-2.95(2H, m), 3.75(4H, t, J=4Hz), 6.20(1H, s), 7.0-7.20(6H, m), 7.44-7.56(2H, m), 7.62(1H, brs), 7.80(1H, brs) 401(M <sup>+</sup> ), 301, 144, 100(100)
6	4		H	Oily	1.45-1.85(10H, m), 2.40-2.60(4H, m), 2.60-3.00(8H, m), 6.20(1H, brs), 7.00-7.40(6H, m), 7.50(2H, d, J=6.3Hz), 7.81(1H, brs), 8.35(1H, brs) 400(M <sup>+</sup> +1), 156, 130, 99, 42(100)



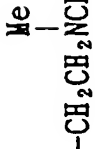

Example No.	n	X	Y	Appearance	PMR (CDCl <sub>3</sub> , δ), MASS(EI)
7	4	$\text{H}$ $-\text{CH}_2\text{CH}_2\text{NCH}_2\text{Ph}$	$-\text{CH}_2\text{CH}_2\text{NECH}_2\text{Ph}$	Oily	1.52(4H, brs), 2.56(4H, brs), 2.90(8H, s), 3.75(4H, s), 6.95-7.40(16H, m), 7.47(2H, d, J=7.8Hz), 8.16(2H, brs) 555(M <sup>+</sup> ), 436, 318(100), 171, 120, 91
8	4	$-\text{CH}_2\text{CH}_2\text{NHCH}_2\text{Ph}$	H	Oily	1.5-1.7(5H, m), 2.5-2.7(4H, m), 2.92(4H, s), 3.74(2H, s), 6.18(1H, s), 6.90-7.30(11H, m), 7.40-7.56(2H, m), 7.62(1H, s), 8.05(1H, s) 421(M <sup>+</sup> ), 302, 144, 120, 91(100)
9	4	$-\text{CH}_2\text{CH}_2\text{N}$ 	$-\text{CH}_2\text{CH}_2\text{N}$ 	Oily	1.55-1.74(4H, m), 2.50-2.86(12H, m), 2.86-3.00(8H, m), 3.70(4H, s), 6.85-7.20(14H, m), 7.49-7.60(2H, m), 7.64-7.74(2H, s) 606(M <sup>+</sup> ), 462, 146(100)
10	4	$-\text{CH}_2\text{CH}_2\text{N}$ 	H	Oily	1.75(4H, m), 2.6-2.86(8H, m), 2.86-3.20(4H, m), 3.74(2H, s), 6.21(1H, s), 6.90-7.30(10H, m), 7.44-7.60(2H, m), 7.70(1H, s), 7.81(1H, brs) 448(M <sup>+</sup> +1), 146(100)
11	4	$-\text{CH}_2\text{CH}_2\text{N}$ 	$-\text{CH}_2\text{CH}_2\text{N}$ 	Oily	1.70(4H, m), 1.82(8H, m), 2.5-2.7(12H, m), 2.75(4H, m), 2.93(4H, t, J=7Hz), 7.08(4H, m), 7.18-7.24(2H, m), 7.52(2H, d, J=7Hz), 8.05(2H, brs) 482(M <sup>+</sup> ), 398, 170, 85(100)



## Example

No.	n	X	Y	Appearance	PMR (CDCl <sub>3</sub> , δ), MASS(EI)
12	4		H	Oily	1.60-1.75(8H, m), 2.50-2.77(10H, m), 2.96(2H, t, J=8Hz), 6.17(1H, s), 6.96-7.14(4H, m), 7.14-7.30(2H, m), 7.42-7.56(2H, m), 8.11(1H, s), 8.29(1H, s) 385(M <sup>+</sup> ), 84(100)
13	4		-CH <sub>2</sub> CH <sub>2</sub> NHCH <sub>2</sub> CH <sub>2</sub> Ph	Oily	1.61(4H, brs), 2.28(2H, brs), 2.68(4H, brs), 2.71(4H, t, J=7Hz), 2.84-2.96(12H, m), 7.04-7.22(16H, m), 7.50(2H, d, J=7Hz), 8.22(2H, s) 581(M <sup>+</sup> -1), 449, 316(100), 134
14	4		-CH <sub>2</sub> CH <sub>2</sub> N	Oily	1.60(4H, brs), 1.85(4H, t, J=6.4Hz), 2.64(4H, s), 2.71(4H, t, J=6.4Hz), 2.96(4H, t, J=7.6Hz), 3.18(4H, t, J=5.6Hz), 3.50(4H, t, J=7.4Hz), 6.52-7.22(14H, m), 7.56(4H, t, J=7.4Hz) 606(M <sup>+</sup> ), 473, 327, 146(100)
15	4		H	Oily	1.6-1.8(4H, m), 1.86(2H, quintet, J=6.2Hz), 2.60-2.82(6H, m), 2.97(2H, t, J=7.5Hz), 3.20(2H, t, J=5.2Hz), 3.51(2H, t, J=7.6Hz), 6.21(1H, s), 6.59(1H, t, J=7Hz), 6.71(1H, d, J=8Hz), 6.97(1H, d, J=7Hz), 7.00-7.16(7H, m), 7.18-7.28(2H, m), 7.67(1H, s), 7.72(1H, brs) 448(M <sup>+</sup> +1), 146(100)

## Example

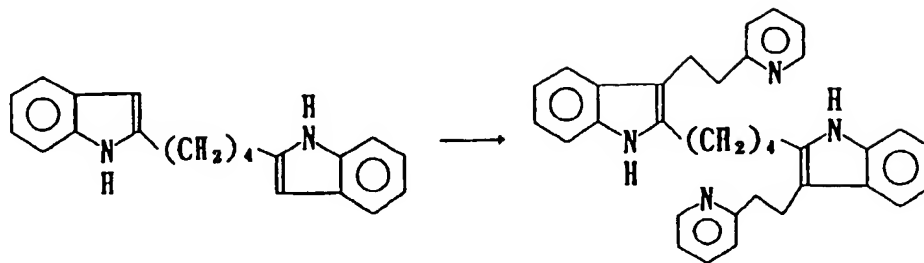
Example No.	n	X	Y	Appearance	PMR (CDCl <sub>3</sub> , δ), MASS(EI)
16	4	-CH <sub>2</sub> CH <sub>2</sub> NHCH <sub>2</sub> CH <sub>2</sub> 	H	Oily	1.58-1.75(5H, m), 2.52-2.74(4H, m), 2.88-3.02(8H, m), 6.20(1H, s), 6.70(1H, s), 7.04-7.34(8H, m), 7.46-7.56(4H, m), 7.62(1H, s), 7.72(1H, brs), 8.33(1H, brs) 476(M <sup>+</sup> +2), 345, 303, 144(100)
17	4	 -CH <sub>2</sub> CH <sub>2</sub> NCH <sub>2</sub> Ph	 -CH <sub>2</sub> CH <sub>2</sub> NCH <sub>2</sub> Ph	Oily	1.58(4H, brs), 2.34(6H, s), 2.59(4H, t, J=8Hz), 2.65(4H, brs), 2.90(4H, t, J=8Hz), 3.56(4H, s), 7.00-7.16(6H, m), 7.20-7.34(10H, m), 7.43(2H, d, J=7.4Hz), 7.62(2H, brs) 582(M <sup>+</sup> ), 461, 135(100)
18	4	 -CH <sub>2</sub> CH <sub>2</sub> NCH <sub>2</sub> Ph	H	Oily	1.56-1.74(4H, m), 2.35(3H, s), 2.56-2.64(2H, m), 2.64-2.74(4H, m), 2.86-2.94(2H, m), 3.58(2H, s), 6.20(1H, s), 7.0-7.34(11H, m), 7.43(1H, d, J=7Hz), 7.51(1H, d, J=7Hz), 7.59(1H, brs), 7.83(1H, brs) 435(M <sup>+</sup> ), 170, 135(100), 92
19	4	-CH <sub>2</sub> CH <sub>2</sub> NH(CH <sub>2</sub> ) <sub>3</sub> Ph	-CH <sub>2</sub> CH <sub>2</sub> NH(CH <sub>2</sub> ) <sub>3</sub> Ph	Oily	1.68(4H, brs), 1.74-2.0(6H, m), 2.55(4H, t, J=7Hz), 2.62(4H, t, J=7Hz), 2.64-2.76(4H, m), 2.82-2.95(8H, m) 610(M <sup>+</sup> ), 288, 144(100)

## Example

No.	n	X	Y	Appearance	PMR (CDCl <sub>3</sub> , δ), MASS(EI)
20	4	-CH <sub>2</sub> CH <sub>2</sub> NH(CH <sub>2</sub> ) <sub>3</sub> Ph	H	Oily	1.58-1.74(4H, m), 1.77(quintet, 2H, J=7Hz), 2.26(1H, brs), 2.53(2H, t, J=7Hz), 2.60(2H, t, J=7Hz), 2.88(2H, d, J=6Hz), 2.92(2H, d, J=6Hz), 6.19(1H, s), 7.00-7.30(11H, m), 7.50(2H, d, J=7Hz), 7.74(1H, brs), 8.39(1H, brs) 450(M <sup>+</sup> ), 303, 148, 91, 44(100)
21	4	-CH <sub>2</sub> CH <sub>2</sub> NH(CH <sub>2</sub> ) <sub>4</sub> Ph	-CH <sub>2</sub> CH <sub>2</sub> NH(CH <sub>2</sub> ) <sub>4</sub> Ph	Oily	1.40-1.62(8H, m), 1.68(4H, brs), 1.78(2H, brs), 2.54(4H, t, J=7Hz), 2.61(4H, t, J=7Hz), 2.70(4H, brs), 2.89(8H, s), 7.00-7.30(16H, m), 7.52(2H, d, J=7Hz), 8.34(2H, s) 639(M <sup>+</sup> +1), 478, 317, 168, 91, 23(100)
22	4	-CH <sub>2</sub> CH <sub>2</sub> NH(CH <sub>2</sub> ) <sub>4</sub> Ph	H	Oily	1.40-1.64(4H, m), 1.64-1.76(5H, m), 2.55(2H, t, J=7Hz), 2.60(2H, t, J=7Hz), 2.66-2.76(4H, m), 2.89(4H, s), 6.19(1H, s), 7.02-7.28(11H, m), 7.52(2H, m), 7.70(1H, brs), 8.30(1H, brs) 463(M <sup>+</sup> ), 302, 162, 91(100)

## Example 23

## 3,3'-Di(2-(2-pyridyl)ethyl)-2,2'-tetramethylenediindole



Tetramethylene-2,2'-bisindole (1.11 g) and 2-vinylpyridine (0.81 g) were added to acetic acid and the mixture was heated at reflux for 8 hrs. Acetic acid was evaporated and chloroform was added to the residue, which was washed with 10% aqueous NaOH solution. Such residue was dried over sodium sulfate and the solvent was evaporated. The crude product was purified by column chromatography on silica gel. Eluates with ethyl acetate afforded 1.39 g of the oily title compound.

PMR (CDCl<sub>3</sub>, δ) 1.47 - 2.08(4H, m), 2.48 - 2.62(4H, m), 3.11(8H, s), 6.95 - 7.22(10H, m), 7.43 - 7.58(4H, m), 8.50 - 8.60(4H, )

MASS(EI) 500(M<sup>+</sup> + 2), 499(M<sup>+</sup> + 1), 407, 219

Further, the following illustrates the H<sup>+</sup>/K<sup>+</sup> ATPase inhibitory activity assay and pharmaceutical preparations of the present compounds.

H<sup>+</sup>/K<sup>+</sup> ATPase Inhibitory Activity Assay

The inhibitory activity was determined in the following manner using H<sup>+</sup>/K<sup>+</sup> ATPase prepared from the stomach of pig.

H<sup>+</sup>/K<sup>+</sup> ATPase dilute solution (100 μl, 50 μg as protein) was added to PIPES-tris (pH 6.2) buffer solution (440 μl) containing 4 mM magnesium chloride and 20 mM potassium chloride. Further, 0.1% ethanol solution of nigericin (5 μl) was added. To the solution was added dimethyl sulfoxide (5 μl) and the mixture was incubated at 37°C for 30 minutes. Then 10 mM PIPES-tris buffer solution (450 μl) containing 4 mM ATP disodium was added to initiate the reaction. 30 minutes later, 50% trichloroacetic acid (1 ml) was added to cease the reaction. The amount of phosphorus released in this reaction was determined by a color development determination at 800 nm according to D. LeBel, et al. method (Anal. Biochem. 85, 86-89), 1978), at which the reading of the absorbance is taken as C1. On the other hand, a similar determination was carried out in the absence of potassium chloride, at which the reading of the absorbance is taken as C2. The inhibitory activity was determined by a similar procedure as in the above reaction, but adding 5 μl of a dimethyl sulfoxide solution containing 1 to 20 mg/ml of the inhibiting substance (test compound), instead of dimethyl sulfoxide. In that case, the readings of the absorbance in the presence and absence of potassium chloride are taken as T1 and T2, respectively.

% Inhibition (I) of the inhibiting substance (test compound) is calculated by the following equation.

$$I = [(C1 - C2) - (T1 - T2)] \times 100 / (C1 - C2)$$

Test Compound	H <sup>+</sup> /K <sup>+</sup> ATPase % Inhibition
Example 1	5% (20 μg/ml)
Example 2	84% (10 μg/ml)
Example 3	97% (10 μg/ml)
Example 4	91% (10 μg/ml)
Example 5	68% (20 μg/ml)

(continued)

Test Compound	H <sup>+</sup> /K <sup>+</sup> ATPase % Inhibition
Example 7	76% (20 µg/ml)
Example 8	100% (20 µg/ml)
Example 13	74% ( 5 µg/ml)
Example 16	71% ( 5 µg/ml)
Example 17	38% ( 5 µg/ml)
Example 18	100% (10 µg/ml)
Example 19	98% (10 µg/ml)

The pharmaceutical preparations of the present compounds are shown below.

#### Pharmaceutical Preparation 1 - Tablets (one tablet)

3,3'-Di(2-phenethylaminoethyl)-2,2'-tetramethylenediindole	10 mg
Lactose	67 mg
Crystalline cellulose	15 mg
Corn starch	7 mg
Magnesium stearate	1 mg

Each ingredient was uniformly blended to prepare powders for direct compression. The powders were formulated by a rotary tableting machine into tablets each 6 mm in diameter and weighing 100 mg.

#### Pharmaceutical Preparation 2 - Granules (one divided form)

A.	3,3'-Di(2-phenethylaminoethyl)-2,2'-tetramethylenediindole	10 mg
	Lactose	90 mg
	Corn starch	50 mg
	Crystalline cellulose	50 mg
B.	Hydroxypropylcellulose	10 mg
	Ethanol	9 mg

The ingredients of A were uniformly blended and the solution of B was added. The mixture was kneaded and granulated by extrusion granulation. The granules were dried in a drier at 50°C and then sieved into the grain size between 297 and 1460 µm. 200 mg of the granules were packed into a unit dosage form.

#### Pharmaceutical Preparation 3 - Syrups

3,3'-Di(2-phenethylaminoethyl)-2,2'-tetramethylenediindole	1.000 g
Refined sugar	30.000 g
D-sorbitol 70 W/V%	25.000 g
Ethyl p-hydroxybenzoate	0.030 g
Propyl p-hydroxybenzoate	0.015 g
Flavor	0.200 g
Glycerol	0.150 g
96% Ethanol	0.500 g
Distilled water	ad lib

The compound, refined sugar, D-sorbitol, ethyl p-hydroxybenzoate and propyl p-hydroxybenzoate were dissolved in 60 ml of warmed water. After cooling, a solution of flavor dissolved in glycerol and ethanol was added. The whole

mixture was diluted with water to balance 100 ml.

#### Pharmaceutical Preparation 4 - Injections

3,3'-Di(2-phenethylaminoethyl)-2,2'-tetramethylenediindole	1 mg
Sodium chloride	10 mg
Distiller water	ad lib

The compound and sodium chloride were dissolved in distilled water to balance 1.0 ml.

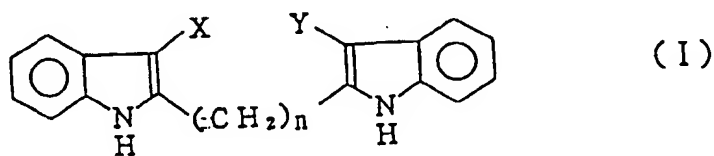
#### Pharmaceutical Preparation 5 - Suppositories

3,3'-Di(2-phenethylaminoethyl)-2,2'-tetramethylenediindole	2 g
Polyethylene glycol	20 g
Glycerol	78 g

Polyethylene glycol 4000 was added to a solution of the compound in glycerol. The mixture was warmed and poured into a suppository mold and then cooled to give suppositories, each weighing 1.5 g.

#### Claims

1. Use of a compound of formula (I)



wherein

X and Y each independently represent H or  $-\text{CH}_2\text{CH}_2\text{R}$ ;

R represents pyridyl or substituted amino of  $\text{NR}_1\text{R}_2$ ;

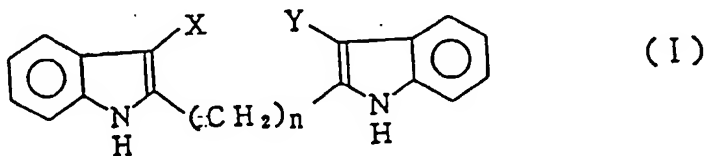
$\text{R}_1$  represents H or  $\text{C}_1\text{-C}_6$  alkyl;

$\text{R}_2$  represents 2-(3-indolyl)ethyl, benzyl, phenylethyl, phenylpropyl or phenylbutyl; or

$\text{R}_1$  and  $\text{R}_2$  together with the nitrogen atom to which they are attached may form an N-containing 5 to 6 membered hetero ring, an N, O-containing hetero ring, which hetero ring may be fused with benzene; n is an integer of 4 to 8;

with the proviso that X and Y both do not represent H or piperidinoethyl when n is 4, or a pharmaceutically acceptable acid addition salt thereof, for the preparation of pharmaceutical compositions for the treatment of ulcers.

2. A compound of formula (I)



wherein

X and Y each independently represent H or  $-\text{CH}_2\text{CH}_2\text{R}$ ;

R represents pyridyl or substituted amino of  $\text{NR}_1\text{R}_2$ ;

$\text{R}_1$  represents H or  $\text{C}_1\text{-C}_6$  alkyl;

$\text{R}_2$  represents 2-(3-indolyl)ethyl, benzyl, phenylethyl, phenylpropyl or phenylbutyl; or

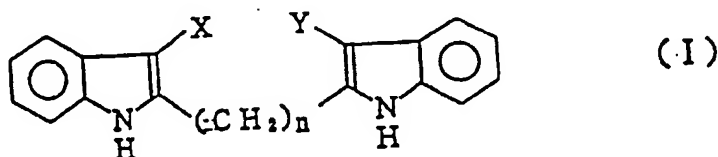
$\text{R}_1$  and  $\text{R}_2$  together with the nitrogen atom to which they are attached may form an N-containing 5 to 6 membered hetero ring, an N, O-containing hetero ring, which hetero ring may be fused with benzene; n is an integer of 4 to 8;

with the proviso that X and Y both do not represent H or piperidinoethyl when n is 4 and that X and Y both do not represent H when n is 5 or 8, or a pharmaceutically acceptable acid addition salt thereof.

3. A compound of claim 2 wherein X represents  $-\text{CH}_2\text{CH}_2\text{R}$ , Y represents H or  $-\text{CH}_2\text{CH}_2\text{R}$  and R represents pyridyl.
4. A compound of claim 2 wherein X represents  $-\text{CH}_2\text{CH}_2\text{R}$ , Y represents H or  $-\text{CH}_2\text{CH}_2\text{R}$ ; R represents substituted amino of  $\text{NR}_1\text{R}_2$ ,  $\text{R}_1$  represents H or  $\text{C}_1\text{-C}_4$  alkyl and  $\text{R}_2$  represents 2-(3-indolyl)ethyl, benzyl, phenylethyl, phenylpropyl and phenylbutyl.
5. A compound of claim 2 wherein X represents  $-\text{CH}_2\text{CH}_2\text{R}$ , Y represents H or  $-\text{CH}_2\text{CH}_2\text{R}$ , R represents substituted amino of  $\text{NR}_1\text{R}_2$ ,  $\text{R}_1$  and  $\text{R}_2$  together with the nitrogen atom to which they are attached form pyrrolidine, piperidine, morpholine, tetrahydroquinoline or tetrahydroisoquinoline.
6. A pharmaceutical composition which comprises as an active ingredient an effective amount of a compound of formula (I) as defined in claims 2 to 5 or a pharmaceutically acceptable acid addition salt thereof and a pharmaceutically acceptable carrier.
7. A pharmaceutical composition of claim 6 for use as an antiulcer agent.

## Patentansprüche

1. Verwendung einer Verbindung der Formel (I)



wobei X und Y jeweils unabhängig H oder  $-\text{CH}_2\text{CH}_2\text{R}$  darstellen;

R Pyridyl oder substituiertes Amino  $\text{NR}_1\text{R}_2$  darstellt;

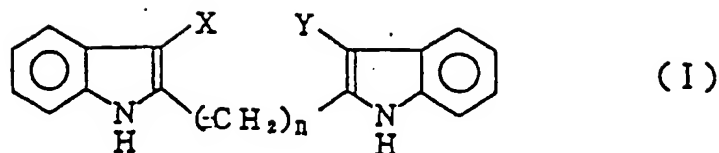
$\text{R}_1$  H oder  $\text{C}_1\text{-C}_6$  Alkyl darstellt;

$\text{R}_2$  2-(3-Indolyl)ethyl, Benzyl, Phenylethyl, Phenylpropyl oder Phenylbutyl darstellt; oder

$\text{R}_1$  und  $\text{R}_2$  gemeinsam mit dem Stickstoffatom, an das sie gebunden sind, einen N-enthaltenden 5- bis 6-gliedrigen Heteroring, einen N,O-enthaltenden Heteroring bilden können, wobei der Heteroring mit Benzol anelliert sein kann; und n eine ganze Zahl von 4 bis 8 ist;

unter der Voraussetzung, daß X und Y beide nicht H oder Piperidinoethyl darstellen, wenn n 4 ist, oder eines pharmazeutisch verträglichen Säureadditionssalzes davon für die Herstellung von pharmazeutischen Zusammensetzungen für die Behandlung von Ulcus.

2. Verbindung der Formel (I)



wobei X und Y jeweils unabhängig H oder  $-\text{CH}_2\text{CH}_2\text{R}$  darstellen;

R Pyridyl oder substituiertes Amino  $\text{NR}_1\text{R}_2$  darstellt;  $\text{R}_1$  H oder  $\text{C}_1\text{-C}_6$  Alkyl darstellt;

$\text{R}_2$  2-(3-Indolyl)ethyl, Benzyl, Phenylethyl, Phenylpropyl oder Phenylbutyl darstellt; oder

$\text{R}_1$  und  $\text{R}_2$  gemeinsam mit dem Stickstoffatom, an das sie gebunden sind, einen N-enthaltenden 5- bis 6-gliedrigen Heteroring, einen

N,O-enthaltenden Heteroring bilden können, wobei der Heteroring mit Benzol anelliert sein kann;

n eine ganze Zahl von 4 bis 8 darstellt;

unter der Voraussetzung, daß X und Y beide nicht H oder Piperidinoethyl darstellen, wenn n 4 ist, und daß X und Y beide nicht H darstellen, wenn n 5 oder 8 ist, oder ein pharmazeutisch verträgliches Säureadditionssalz davon.

3. Verbindung nach Anspruch 2, wobei X  $-\text{CH}_2\text{CH}_2\text{R}$  darstellt, Y H oder  $-\text{CH}_2\text{CH}_2\text{R}$  darstellt und R Pyridyl darstellt.

4. Verbindung nach Anspruch 2, wobei X  $-\text{CH}_2\text{CH}_2\text{R}$  darstellt, Y H oder  $-\text{CH}_2\text{CH}_2\text{R}$  darstellt; R substituiertes Amino  $\text{NR}_1\text{R}_2$  darstellt,  $\text{R}_1$  H oder  $\text{C}_1\text{-C}_4$  Alkyl darstellt und  $\text{R}_2$  2-(3-Indolyl)ethyl, Benzyl, Phenylethyl, Phenylpropyl und Phenylbutyl darstellt.

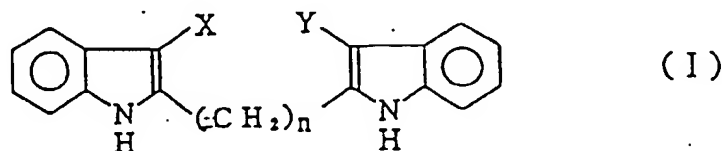
5. Verbindung nach Anspruch 2, wobei X  $-\text{CH}_2\text{CH}_2\text{R}$  darstellt, Y H oder  $-\text{CH}_2\text{CH}_2\text{R}$  darstellt; R substituiertes Amino  $\text{NR}_1\text{R}_2$  darstellt, und  $\text{R}_1$  und  $\text{R}_2$  gemeinsam mit dem Stickstoffatom, an das sie gebunden sind, Pyrrolidin, Piperidin, Morpholin, Tetrahydrochinolin oder Tetrahydroisochinolin darstellen.

6. Pharmazeutische Zusammensetzung, die als aktiven Bestandteil eine wirksame Menge einer Verbindung der Formel (I) wie in Ansprüchen 2 bis 5 definiert oder ein pharmazeutisch verträgliches Säureadditionssalz davon und einen pharmazeutisch verträglichen Träger umfaßt.

7. Pharmazeutische Zusammensetzung nach Anspruch 6 zur Verwendung als Anti-Ulcus-Mittel.

## Revendications

1. Utilisation d'un composé de formule (I)



dans laquelle X et Y représentent chacun indépendamment H ou  $-\text{CH}_2\text{CH}_2\text{R}$  ;

R représente un groupe pyridyle ou amino substitué de formule  $\text{NR}_1\text{R}_2$  ;

$\text{R}_1$  représente H ou un groupe alkyle en  $\text{C}_1\text{-C}_6$  ;

$\text{R}_2$  représente un groupe 2-(3-indolyl)éthyle, benzyle, phényléthyle, phénylpropyle ou phénylbutyle ; ou

$\text{R}_1$  et  $\text{R}_2$  conjointement avec l'atome d'azote auquel ils sont fixés, peuvent former un hétérocycle azoté avec de 5 à 6 chaînons, un hétérocycle contenant N, O, cet hétérocycle pouvant être fusionné avec le benzène ;

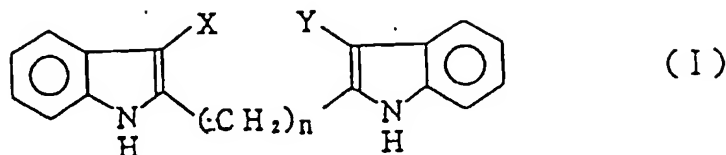
n représente un nombre entier valant de 4 à 8 ;

à la condition que X et Y ne représentent pas tous les deux H ou un groupe pipéridinoéthyle lorsque n vaut 4, ou d'un de ses sels d'addition d'acides pharmaceutiquement acceptables, pour la préparation de compositions phar-



maceutiques pour le traitement des ulcères.

2. Composé de formule (I)



dans laquelle X et Y représentent chacun indépendamment H ou  $-\text{CH}_2\text{CH}_2\text{R}$  ;

R représente un groupe pyridyle ou amino substitué de formule  $\text{NR}_1\text{R}_2$  ;

$\text{R}_1$  représente H ou un groupe alkyle en  $\text{C}_1\text{-C}_6$  ;

$\text{R}_2$  représente un groupe 2-(3-indolyl)éthyle, benzyle, phényléthyle, phénylpropyle ou phénylbutyle ; ou

$\text{R}_1$  et  $\text{R}_2$ , conjointement avec l'atome d'azote auquel ils sont fixés, peuvent former un hétérocycle azoté avec de 5 à 6 chaînons, un hétérocycle contenant N, O, cet hétérocyclique pouvant être fusionné avec le benzène ;

n représente un nombre entier valant de 4 à 8 ;

à la condition que X et Y ne représentent pas tous les deux H ou le groupe pipéridinoéthyle lorsque n vaut 4 et que X et Y ne représentent pas tous les deux H lorsque n vaut 5 ou 8 ; ou un de ses sels d'addition d'acides pharmaceutiquement acceptables.

3. Composé selon la revendication 2, dans lequel X représente  $-\text{CH}_2\text{CH}_2\text{R}$ , Y représente H ou  $-\text{CH}_2\text{CH}_2\text{R}$  et R représente le groupe pyridyle.
4. Composé selon la revendication 2, dans lequel X représente  $-\text{CH}_2\text{CH}_2\text{R}$ , Y représente H ou  $\text{CH}_2\text{CH}_2\text{R}$  ; R représente un groupe amino substitué de formule  $\text{NR}_1\text{R}_2$ ,  $\text{R}_1$  représente H ou un groupe alkyle en  $\text{C}_1\text{-C}_4$  et  $\text{R}_2$  représente un groupe 2-(3-indolyl)éthyle, benzyle, phényléthyle, phénylpropyle et phénylbutyle.
5. Composé selon la revendication 2, dans lequel X représente  $-\text{CH}_2\text{CH}_2\text{R}$ , Y représente H ou  $-\text{CH}_2\text{CH}_2\text{R}$ , R représente un groupe amino substitué de formule  $\text{NR}_1\text{R}_2$ ,  $\text{R}_1$  et  $\text{R}_2$  conjointement avec l'atome d'azote auquel ils sont fixés forment le cycle pyrrolidine, pipéridine, morpholine, tétrahydroquinoléine ou tétrahydroisoquinoléine.
6. Composition pharmaceutique qui comprend, à titre de principe actif, une quantité efficace d'un composé de formule (I) tel que défini dans les revendications 2 à 5 ou un de ses sels d'addition d'acides pharmaceutiquement acceptables et un véhicule pharmaceutiquement acceptable.
7. Composition pharmaceutique selon la revendication 6, à utiliser à titre d'agent anti-ulcéreux.